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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,955	12/13/2001	James R. Lupski	HO-P02086US1	2699

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FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,955	LUPSKI ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *2,6 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,35-40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The response to restriction requirement (Paper No. 9) filed on June 7, 2003 has been entered and considered.

2. The Information Disclosure Statement (Paper No. 6) filed on November 20, 2002 has been entered and considered.

3. Applicant's election with traverse of Group IX (claims 35-40 with respect to a species (274 ΔC) in Paper No. 9 is acknowledged. Applicants' request for rejoinder of Group I and IX is fully considered and found persuasive. Applicants' election of SEQ ID No. 76 is fully considered, however, Examiner would like to reinstate that the election of one SED ID. NO. is not a species election rather, it is the election of a restricted SEQ ID No. corresponding to an elected group.

4. Claims 1, 3-5, 7, 35-40 in Groups I and IX and the newly added claim 42 are considered for examination in this office action with respect to SEQ ID No. 76 and the species 274ΔC. Claims 2, 6 and the newly added claim 41are withdrawn from consideration since these claims are dependent on non-elected SEQ ID Nos. and non-elected species.

5. The instant application has filing date as December 13, 2001 and claims priority date to a provisional application No. 60/255,217 filed on December 13, 2000 (see page 1, paragraph 2, lines 1-2 of the specification). However the Oath / Declaration is defective in not claiming the priority.

6. The disclosure is objected because of the following informalities:

Oath / Declaration

(i) It does not identify the mailing or post office address of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail

and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

(ii) The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a). The priority data specified in the specification is not identified in the Oath/ Declaration.

Specification

(iii) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code (see at least page 15, lines 14, 17-21). See MPEP § 608.01.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7, 35-40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limitaed to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance

Presence and Absence of Working Examples

Nature of Invention

Level of Predictability and unpredictability in the art

Nature of the Invention :

Claims 1, 3-5, and 7 are drawn to a method of diagnosing myelinopathy in an individual and claims 35-40, and 42 are drawn to a method of detecting the presence or absence of any mutation in a periaxin polynucleotide and its association with any myelinopathy. Further, Claim 7 is drawn to a specific alteration in a periaxin polynucleotide and Claim 36 is drawn to an association between a specific mutation in periaxin and any myelinopathy. Claims 4 and 40 are broadly drawn to a broad range of diseases of myelinopathy such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS).

Amount of Direction and Guidance:

The specification discloses the identity of several mutations in periaxin polynucleotide and their locations (see Figs. 4 and 9). The specification on page 14, asserts a correlation between the human orthologue of murine and rat periaxin (Prx) with human inherited myelinopathy and further asserts that human periaxin gene which encodes two PDZ-domain proteins, is required for the maintenance of peripheral nerve myelin. The specification teaches that based on knockout animal models, periaxin is correlated to the proper formation of myelin sheaths and the specification broadly discloses the identification of recessive Prx mutations comprising nonsense

and frame shift mutations in the periaxin gene. The specification asserts that based on the common known methods in the art, mutations in other periaxin polynucleotide sequences (for example SEQ ID No. 76) could be detected. The specification discloses mutations in SEQ ID No.1 and extrapolates the use of similar techniques to detect mutations in other periaxin polynucleotides (for example SEQ ID NO.76). The specification discloses mutations in other genes associated with some myelinopathy (see page 20) (such as DNA rearrangements in CMT patients caused by mutations in MPZ, Cx32, EGR2, and mutations in MPZ and EGR2 in DSS patients). Further the specification on page 21, asserts the function of periaxin in the maintenance of the myelin sheath based on animal studies. However, the specification has not established that a statistically significant association exists between all of the specific mutations disclosed in the specification, and any myelinopathy, or any specific myelinopathy, or that a predictable correlation can be made as to an association between any mutation in the periaxin gene and any mylenopathy or any specific myelinopathy.

Presence and Absence of working examples:

The specification discloses a method of screening Prx mutations in some family studies and detected mutations comprising a deletion and a transition in the affected patients with peripheral neuropathy. The specification correlates the mutations with the loss of function of Prx gene in relation to studies in rat (example 4). The examples 2-4 in the specification establish a positive correlation between the presence of a periaxin polynucleotide comprising mutation which results in a truncated periaxin polypeptide in patients with undisclosed myelinopathy, wherein said patients have two aberrant forms of periaxin polypeptides. Although the specification does not demonstrate such, the specification asserts that the mutations could be associated with loss of

function of the periaxin polypeptide. It is noted, however, that these examples also establish that the mere presence of a mutation (i.e., only a single copy) is NOT associated with the disease as in HOU579 family, wherein the unaffected parents had a single mutant polynucleotide and a wild type polynucleotide. Further there is no description of the type of peripheral neuropathy of the affected patients. (see page 65, example 3). Further examples in the specification merely assert s correlation between mutations in Prx with myelinopathy in general, however no specific mutation is associated with any of the different types of myelinopathies as exemplified by the example 8 in the specification (see page 72). Further table- 2 shows that the unaffected control subjects contain mutations in periaxin. The specification does not teach whether the mutations in table-2 are associated with loss of function or if they are statistically associated with any specific peripheral neuropathy or any specific myelinopathy.

Level of Predictability and unpredictability in the art :

Predictability in the art suggests mutations in genes other than the specific periaxin gene, are associated with specific type of myelinopathy, for example Boss et al. (USPN. 5,691,144) teaches mutations in connexin-32 are associated with X-linked Charcot-Marie-Tooth (CMT) disease, Timmermann et al. (Neurology, Vol. 52, pp. 1827-1832, 1999) teach a missense mutation in EGR2 gene in association with Dejerine-Scottas syndrome (DSS). Lupski et al. (USPN. 5,780,223) teach DNA duplication in CMT1A gene sequence association with autosomal dominant CMT disease, and Roa et al. (Nature Genetics, Vol. 5, pp. 269273, 1993) teach that some point mutations in peripheral myelin protein 22 (PMP22) gene are associated with CMT1A, while others are associated with DSS (Fig.3, page 271). With regards to the specific periaxin gene Guilbot et al. (Human Molecular Genetics, Vol. 10, No.4, 2001), teach

periaxin is responsible for CMT4F, an autosomal recessive form of CMT disease, and Gillepsie et al. (Neuron, Vol. 12, pp. 497-508, 1994) teach role of periaxin in rat pheripheral nervous system and discloses that periaxin localization in schwann cells and its possible role in ensheathment. However, the art does not establish a predictable association that any specific mutation in periaxin or any other genes is predictably associated with all of the large number of diseases encompassed by the recitation of "myelinopathy". For example Roa et al. teach that while some point mutations in PMP22 are associated with CMT1A, others are associated with DSS. The art is further silent with regard to a predictable association between any specific mutation in periaxin and a representative number of diseases encompassed by the term "myelinopathy". Diseases encompassed by the term "myelinopathy" include a large number of heterogeneous diseases with differing symptoms and associations to genetic mutations. To date, however, there is no evidence that the association of a mutation in a specific gene and a specific form of myelinopathy can predictably correlate the presence of any other, or all, specific myelinopathy encompassed by the broad term "myelinopathy". The claims further broadly encompass detecting an association between any specific mutation in periaxin, and an association to a specific unnamed myelinopathy. The specification, however does not establish a statistically significant association with any of the disclosed mutations in periaxin, and any specific form of myelinopathy such that the skilled artisan might be able to predictably correlate which mutations in periaxin would be associated with a specific form of myelinopathy. Furhter, to date, no teaching is available in the art with regards to a universal correlation between any mutation in periaxin and an association with any general or specific type of myelinopathy. It is apparent from the prior art that the unpredictability is high and the instant specification fails to

teach any particular mutation associated with any particular type of myelinopathy. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of any particular mutation in periaxin with any particular type of myelinopathy. Further, CMT is inherited in three forms, i.e., autosomal dominant, autosomal recessive and X-linked conditions. The specification fails to support an association of a mutation in periaxin with all the three forms of CMT.

In addition, the specification does not establish the identity of any specific critical nucleotide or amino acid alteration(s) that are associated with loss of function or are associated with myelinopathy. The missense mutations in table-2 were also found in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or compound heterozygous for other mutations in periaxin. It is clear from the teachings in table-2, that the mere presence of an alteration in periaxin such as a substitution or deletion is not indicative of myelinopathy. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear whether these mutations or any specific mutation will have a significant affect or not.

Quantity of Experimentation Necessary:

Given the lack of guidance in the specification and the unpredictability in the art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that any mutation in periaxin is significantly associated with any specific myelinopathy. To practice the invention

as claimed, the skilled artisan would have to perform a large study of patients with different types of myelinopathy, such as CMT, DSS, and matched controls to determine if any general alteration or mutation in periaxin or any specific claimed alteration or mutation in periaxin, was associated with any specific myelinopathy. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art. Therefore, given the lack of guidance from the specification as to any statistical association between the claimed association of any mutation in periaxin polynucleotide and any myelinopathy, and the unpredictability taught in the art as to some point mutations in other genes such as PMP22 are associated with one form of CMT, while other mutations in the same PMP22 are associated with DSS, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
July 22, 2003

JEHANNE SOUAYA
PATENT EXAMINER
Primary
Jehanne Souaya
July 22, 2003